

2/8/01  
This Application is a continuation-in-part of Serial No. 08/827,230,  
Filed April 2, 1997, now U.S. Patent No. 5,908,850 which is,

**PHENIDATE DRUG FORMULATIONS HAVING  
DIMINISHED ABUSE POTENTIAL**

This application is a continuation-in-part of  
Serial No. 08/567,131 filed December 4, 1995, <sup>now abandoned</sup> and Serial No.  
5 08/583,317, filed January 5, 1996, <sup>now U.S. Patent No. 5,733,756</sup> both assigned to the  
assignee hereof. The foregoing applications are incorp-  
orated herein by reference.

**FIELD OF THE INVENTION**

The present invention relates to phenidate drug  
10 compositions for treating certain Central Nervous System  
disorders such as Attention Deficit Disorder (ADD),  
Attention Deficit Hyperactivity Disorder (ADHD), HIV/AIDS  
cognitive decline, and AIDS Dementia Complex. This  
invention features such drugs having decreased side effects,  
15 reduced euphoric effect, and reduced drug abuse potential.

**BACKGROUND OF THE INVENTION**

Attention Deficit Disorder (ADD) is the most  
commonly diagnosed nervous system illness in children.  
Patrick et al., J. Pharmacol. & Exp. Therap., 241:152-158  
20 (1987). Symptoms of ADD include distractibility and  
impulsivity. A related disorder, termed Attention Deficit  
Hyperactivity Disorder (ADHD), is further characterized by  
increased symptoms of hyperactivity in patients. Racemic  
methylphenidate (e.g., Ritalin®) is a mild Central Nervous  
25 System stimulant with pharmacological activity qualitatively  
similar to amphetamines, and has long been the drug of  
choice for symptomatic treatment of ADD in children.

Greenhill, L., Child & Adol. Psych. Clin. N.A., Vol. 4, Number 1:123-165 (1995).

Current administration of racemic methylphenidate, however, often results in notable side effects such as  
5 anorexia, weight loss, insomnia, dizziness and dysphoria. Additionally, racemic methylphenidate, which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for substance abuse in patients.

10 At least 70% of HIV-infected individuals who have developed Acquired Immunodeficiency Syndrome (AIDS) eventually manifest cognitive defects, and many display signs and symptoms of dementia. See Navia et al., *Annals of Neurology*, 19:517-524 (1986). Complaints of forgetfulness, loss  
15 of concentration, fatigue, depression, loss of attentiveness, mood swings, and thought disturbance are common in patients with Human Immunodeficiency Virus (HIV) disease. Douzenis et al., *Proc. 7th Int'l. Conf. AIDS*, 1, MB, 2135:215 (1991); Holmes et al., *J. Clin. Psychiatry*,  
20 50:5-8 (1989). Racemic methylphenidate has been used to treat cognitive decline in AIDS/ARC patients. Brown, G., *Intl. J. Psych. Med.* 25(1): 21-37 (1995). As described above, racemic methylphenidate, a Schedule II controlled substance, produces a euphoric effect when administered  
25 intravenously or through inhalation, and thus carries a high potential for drug abuse.

U.S. Patent 2,507,631, to Hartmann et al. describes methylphenidate and processes for making the same. U.S. Patent 2,957,880, to Rometsch et al. describes the  
30 conversion of  $\alpha$ -aryl- $\alpha$ -piperidyl-(2)-acetic acids and derivatives thereof (including methylphenidate) into their respective racemates. Each of these patents is incorporated herein by reference.

Holmes et al., *J. Clin. Psychiatry*, 50:5-8 (1989)  
35 reported on the use of racemic methylphenidate (Ritalin®) and dextroamphetamines in the treatment of cognitive impairment in AIDS patients.

Srinivas et al., *J. Pharmacol. & Exp. Therap.*, 241:300306 (1987) described use of racemic dl-threo-methylphenidate (Ritalin®) in the treatment of ADD in children. This study noted a 5-fold increase in plasma  
5 levels of d-threo-methylphenidate in children treated with racemic methylphenidate, but was otherwise inconclusive with regard to the efficacy of a single methylphenidate isomer at therapeutically significant doses.

Srinivas et al., *Clin. Pharmacol. Ther.*, 52:561-  
10 568 (1992) studied the administration of dl-threo, d-threo and l-threo-methylphenidate to children suffering from ADHD. While Srinivas et al. reported the pharmacodynamic activity of dl-threo-methylphenidate resides in the d-threo isomer, this study investigated neither the adverse side effects of  
15 the l-threo isomer, nor the euphoric effects of the single isomers or racemate. Single isomer dosages below 1/2 of the racemate dosage were not studied.

Patrick et al., *J. Pharmacol. & Exp. Therap.*, 241:152158 (1986) examined the pharmacology of the  
20 enantiomers of threo-methylphenidate, and assessed the relative contribution of each isomer to central and peripheral actions of Ritalin®.

Brown, G., *Intl. J. Psych. Med.*, 25 (1) :21-37 (1995) reported the use of racemic methylphenidate for the  
25 treatment of AIDS 'cognitive decline.

Patrick et al., *Psychopharmacology: The Third Generation of Progress*, Raven Press, N.Y. (1987) examined the pharmacokinetics and actions of methylphenidate in the treatment of Attention Deficit Hyperactivity Disorder  
30 (ADHD). Patrick noted the d-threo isomer possesses higher activity than the l-threo isomer, and that d-threo methylphenidate may be responsible for the therapeutic activity in the racemic drug.

Aoyama et al., *Clin. Pharmacol. Ther.*, 55:270-276  
35 (1994) reported on the use of (+)-threo-methylphenidate in the treatment of hypersomnia. Aoyama et al. describe a correlation between sleep latency in patients and plasma

concentration of (+)-threo-methylphenidate.

Glutathione is an important antioxidative agent that protects the body against electrophilic reactive compounds and intracellular oxidants. It has been

5 postulated that HIV-AIDS patients suffer from drug hypersensitivity due to drug overload and an acquired glutathione deficiency. See Uetrecht et al., *Pharmacol. Res.*, 6:265-273 (1989). Patients with HIV infection have demonstrated a reduced concentration of glutathione in

10 plasma, cells and broncho-alveolar lavage fluid. Staal et al., *Lancet*, 339:909-912 (1992). Clinical data suggests that HIV-seropositive individuals display adverse reactions to the simultaneous administration of several otherwise therapeutic drugs. Rieder et al., *Ann. Intern. Med.*,

15 110:286-289 (1989). It is desirable to provide for the administration of methylphenidate in reduced dosages among patients with drug hypersensitivity due to HIV infection.

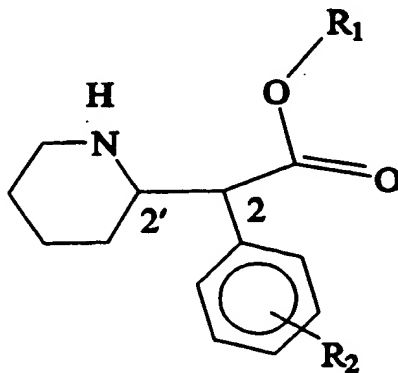
There is a long-felt and very intense need for phenidate drug compositions, especially methyl phenidate,

20 which are less susceptible to unlawful abuse and which exhibit diminished side effects while retaining therapeutic efficacy.

#### SUMMARY OF INVENTION

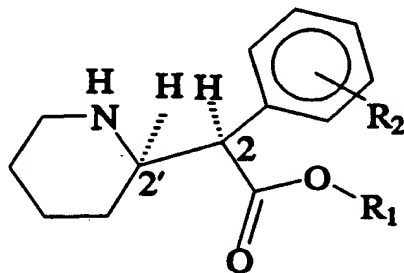
Phenidate drugs in accordance with this invention

25 have the structure:

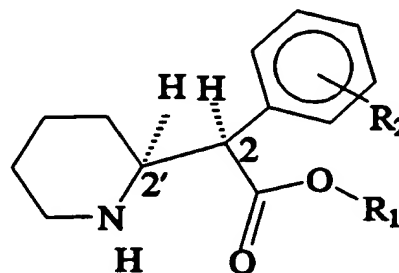


where  $R_1$  is  $C_1 - C_4$  alkyl and  $R_2$  is either  $C_1 - C_4$  alkyl or hydrogen. Of this family of drugs, methylphenidate, where  $R_1$  is methyl and  $R_2$  is hydrogen, is the most well known, having long been prescribed under the trade mark Ritalin®.

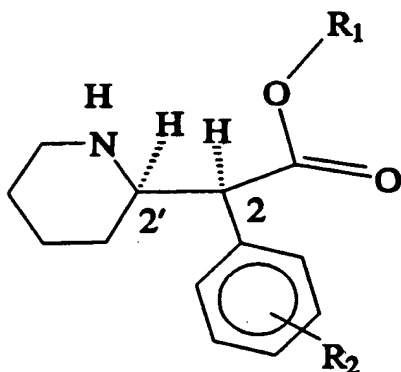
- 5 Phenidate drugs are  $\alpha$ -aryl- $\alpha$ -piperidyl-2-acetic acids and comprise two centers of asymmetry, existing as four separate optical isomers as follows:



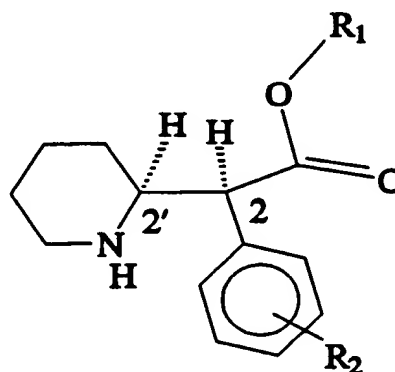
2R,2'R; D-THREO



2R,2'S; D-ERYTHRO



2S,2'R; L-ERYTHRO



2S,2'S; L-THREO

- It is known that certain physiological properties of methylphenidate and other phenidate drugs are dependent upon stereochemistry. Thus, while the threo racemate of methylphenidate is understood to produce the desired central nervous system action, the erythro racemate is thought to contribute to hypertensive side effects.
- 10

It is now believed, however, that another stereochemical distinction also applies. Studies in animals, children and adults have demonstrated pharmacological activity in the D-threo isomer of methylphenidate (2R,2'R). See Patrick et al., *J. Pharmacol. & Exp. Therap.*, 241:152-158 (1987). The role of the L-threo isomer in toxicity or adverse side effects has not been examined heretofore although the potential for isomer ballast in methylphenidate and other phenidate drugs is of concern for many patient groups, particularly those drug hypersensitive patients as described above.

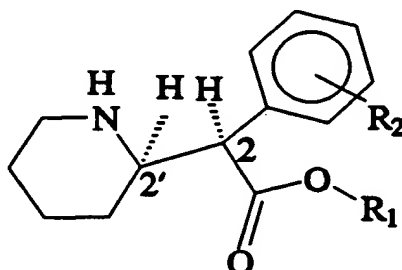
Although L-threo-methylphenidate is rapidly and stereoselectively metabolized upon oral administration by extensive first pass metabolism, intravenous administration or inhalation results in high L-threo methylphenidate serum levels. Srinivas et al., *Pharmacol. Res.*, 10:14-21 (1993). Intravenous administration and inhalation are methods of choice by drug abusers of current, racemic methylphenidate formulations. It is now believed that the euphoric effect produced by current formulations of methylphenidate is due to the action of L-threo-methylphenidate, rather than the pharmaceutically efficacious D-threo compound.

Accordingly, it has now been discovered that the incorporation into pharmaceutical formulations of the D-threo isomer (2R,2'R) of a phenidate drug, especially methylphenidate, with the substantial exclusion of the other three isomers of the phenidate, especially the L-threo isomer, produces a phenidate medication dosage form which retains high pharmaceutical efficacy levels upon administration to patients, while simultaneously possessing fewer or reduced side-effects, reduced euphoric effect and reduced potential for abuse.

Patients suffering from Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS cognitive decline, and AIDS Dementia Complex are benefitted by receiving phenidate drug, especially the preferred methylphenidate, in a dosage form which substantially

excludes three of the four stereoisomers, D erythro, L erythro, and L-threo. Stated alternatively, such dosage forms comprise D-threo phenidate in the substantial absence of L-threo and both erythro stereoisomers.

5 The present invention also provides dosage forms of phenidate drugs for treating Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder in children and adults while providing for reduced side effects, reduced euphoric effect and reduced potential for abuse. This is  
10 accomplished by formulating dosage forms for administration to patients comprising D-threo-phenidate or a pharmaceutically acceptable salt thereof, substantially free of the L-threo isomer and both erythro isomers. The invention further provides methods of treating AIDS-related  
15 dementia and related cognitive disorders while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential comprising administering D-threo-phenidate (2R,2'R) of the formula:



or a pharmaceutically acceptable salt thereof, substantially  
20 free of the other three stereoisomeric forms of the drug.

In accordance with the invention, R<sub>1</sub> is methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl or tert-butyl. It is preferred that R<sub>1</sub> be methyl. R<sub>2</sub> may be hydrogen, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl or tert-  
25 butyl and may appear either ortho, meta or para to the acetic acid moiety. Additional substituents may also appear in the phenidate drug molecule, either in the aryl

✓ ring, in the piperidine heterocycle of in the ester function, however, extensive substitution is not preferred.

Salts of phenidates, such as the conventional hydrochloride salts, are also within the spirit of the

5 invention and all such salts are specifically contemplated hereby.

Preferably,  $R_1$  is methyl and  $R_2$  is hydrogen such that the phenidate drug is methylphenidate.

Prescription of methylphenidate to treat AIDS  
10 cognitive decline and AIDS Dementia Complex associated with HIV infection is becoming increasingly popular. However, high doses in excess of 40 mg/day are not well tolerated by a substantial number of HIV-infected patients when treated over weeks or months. Brown, G., *Int'l J. Psychiatry*.  
15 *Med.*, 25:21-37 (1995). The exclusive D-threo isomer formulations of the present invention enable a lowered dosing therapy with avoidance of the administration of the stereoisomer believed to be responsible for adverse side effects and abuse potential resulting in improved efficacy  
20 for diseased patients and particularly HIV-infected patients.

Racemic methylphenidate and its individual isomers are known. See U.S. Patent Nos. 2,507,631 and 2,957,880. They can be prepared by conventional techniques, and can be  
25 obtained from a variety of commercial sources. Moreover, the D-threo- isomer of methylphenidate and other phenidate drugs can be prepared in accordance with Serial No. 08/583,317 filed January 5, 1996, which application forms a parent to this application and has been incorporated herein  
30 by reference. Examples forming part of this application set forth certain preferred synthetic routes to the phenidate compounds useful in the practice of this invention. Persons of ordinary skill will be able to modify such procedures to prepare the lower alkyl substituted phenyl derivatives and  
35 lower alkyl esters contemplated herein without undue experimentation. Thus, preparation of ethyl, propyl, isopropyl etc. esters is a simple matter in view of the



synthetic schemes set forth. Likewise, substituting the phenyl ring with one or more alkyl or other substituents may also be accomplished.

5 The dosage forms of the present invention can be administered orally, rectally, parenterally, or transdermally, alone or in combination with other psychostimulants, antidepressants, and the like to a patient in need of treatment. Oral dosage forms include tablets, capsules, dragees, and other conventional, pharmaceutical  
10 forms. Isotonic saline solutions, conveniently containing about 1-40 milligrams of drug per milliliter can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes. Rectal administration can conveniently be effected through the use  
15 of suppositories such as can easily be formulated from conventional carriers such as cocoa butter. Transdermal administration can be effected through the use of transdermal patch delivery systems and the like. The preferred routes of administration are oral and parenteral.

20 The dosage employed should be carefully titrated to the patient, considering age, weight, severity of the condition, and clinical-profile. Typically, the amount of d-threo-methylphenidate administered will be in the range of 1-50 mg/day, but the actual decision as to dosage will  
25 depend upon the exact phenidate drug being employed and will be made by the attending physician as a matter of routine. Such physician can, however, determine an appropriate regime employing well-known medical considerations. Such persons will appreciate that the overall dosage amount will be  
30 significantly smaller than that used with the corresponding racemic drug, since the undesired enantiomers are not included in the present dosage forms.

Accordingly, a pharmaceutically effective amount of a phenidate drug in accordance with this invention will  
35 be understood by persons of ordinary skill in the art to be that amount of the selected D-threo phenidate which, upon administration to a patient, would result in a sensible and

therapeutically useful effect.

When phenidates other than methylphenidate are to be administered, it will be appreciated that the effective amount of drug will likely be different than for  
5 methylphenidate. Determination of such amount, however, is well within the routine skill of the practitioner. In accordance with preferred embodiments, from 1 to about 50 mg will be administered to patients, with from about 2 to about 20 mg per day being still more preferred. In still more  
10 preferred embodiments, patients will receive from about 2½ to about 12 mg per day.

It is desirable to provide unit dosage forms for administration of compounds of the invention comprising from about 1 to about 50 mg of drug, with amounts of from about 2  
15 to about 20 and particularly from about 2½ to about 12 mg being still more preferred. Oral administration is the protocol of choice, however other routes of administration, such as intravenous, intraperitoneal, rectal and the like may also be employed in formulating the unit dosage forms of  
20 this invention. Carriers, diluents and excipients are conventionally employed in formulating unit dosage forms and the same are selected as a matter of routine depending upon the selected route of administration. For oral administration, formulation into tablets using tableting  
25 excipients are conveniently employed, although capsular and other oral forms are also useful.

The present invention provides enhanced relief for patients suffering from Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder while providing for  
30 reduced side effects, reduced euphoric effect, and reduced abuse potential through administration of D-threo-methylphenidate substantially free of the L-threo and other isomers. The invention gives rise to methods of treatment of AIDS related dementia and related cognitive disorders  
35 with D-threo-methylphenidate substantially free of the remaining isomers.

✓ The term, "substantially free as it applies to a

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stereoisomer in accordance with a composition of this invention means that the composition contains no more than 10% by weight of the isomer in question. It is preferred that such composition have less than about 2% of the  
5 unwanted isomers and even more preferred that less than 1% be present. When applied to a plurality of stereoisomers, then all of the isomers, taken together, comprise no more than 10% by weight of the composition and preferably less than 2%. It is preferred that compositions characterized as  
10 being "substantially free" of all stereoisomers but the D-threo isomer comprise no more than about 5% of other isomers. It is still more preferred that no more than 1% of the undesired isomers be present.

The following examples will serve to further  
15 typify the nature of the invention, but should not be construed as a limitation on the scope thereof, which is defined solely by the appended claims.

#### EXAMPLES

A suitable salt medium for the microbiological  
20 transformations described in the following examples has been denominated "media A" and has the following composition:

	MgSO <sub>4</sub>	1.00	g/L
	CaCl <sub>2</sub>	0.021	g/L
	ZnSO <sub>4</sub> ·7H <sub>2</sub> O	0.20	mg/L
25	MnSO <sub>4</sub> ·4H <sub>2</sub> O	0.10	mg/L
	H <sub>3</sub> BO <sub>3</sub>	0.02	mg/L
	CUSO <sub>4</sub> ·5H <sub>2</sub> O	0.10	mg/L
	CoCL <sub>2</sub> ·6H <sub>2</sub> O	0.05	mg/L
	NiCl <sub>2</sub> ·6H <sub>2</sub> O	0.01	mg/L
30	FeSO <sub>4</sub>	1.50	mg/L
	NaMoO <sub>4</sub>	2.00	mg/L
	Fe EDTA	5.00	mg/L
	KH <sub>2</sub> PO <sub>4</sub>	20.00	mg/L
	NaOH	to pH 7	

**EXAMPLE 1**

Preparation of D-threo-2-(piperid-2-yl)-2-phenyl-acetic acid from trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one

**Preparation of Biocatalyst**

5 Lactamase is obtained from *Pseudomonas cepacia* grown on 1-2% penicillin as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 2 g/l of penicillin is inoculated with *Pseudo-*  
10 *monas cepacia*. After the mixture is incubated at 30° C for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with 2 g/l penicillin. After 40 hours of incubation at 30° C, the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml  
15 phosphate buffer pH 7 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

20 Racemic (+/-)trans-7-phenyl-1-azabicyclo(4,2,0)octan-8-one (0.5 g) is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 7 and 1 ml cell extract of lactamase. The reaction is maintained at 30° C until the enantiomer excess as determined by chiral  
25 chromatography is no less than 98% of D-ritalinic acid, generally about 3 hours under these conditions. A lactamase with opposite stereoselectivity obtained from a microorganism such as *Rhodococcus rhodochrous* can be used to resolve (+/-)trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one  
30 to L-ritalinic acid and the D-trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one. This lactam is then hydrolyzed to the D-ritalinic acid by conventional means.

Trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one may be prepared by the method of Corey, Mol, or Earle (Corey et  
35 al., *J. Amer. Chem. Soc.*, 87:2518 (1965); Earle et al., *J. Chem. Soc. C.*, 2093 (1969); Moll F. *Naturforsch.*, Teil B, 21:297 (1966).

## Isolation of D-lactam

The reaction mixture prepared above is extracted with methylene chloride and the organic layer is dried with  $\text{MgSO}_4$ . The organic layer is then filtered and concentrated by rotary evaporation at  $30^\circ$  with reduced pressure, to yield an oil product. The oil product may be further purified by column chromatography.

## EXAMPLE 2

Preparation of D-threo-2-(piperid-2-yl)-2-phenylacetic acid from threo-2-(piperid-2-yl)-2-phenyl-2-acetamide

## Preparation of Amidase

Amidase is obtained from *Acinetobacter baumannii* grown on 30 mM 2-cyanobutane as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 30 mM 2-cyanobutane is inoculated with *Acinetobacter baumannii*. After the mixture is incubated at  $30^\circ \text{C}$  for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with 30 mM 2-cyanobutane. After 40 hours of incubation at  $30^\circ \text{C}$ , the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer pH 7.5 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

Racemic threo-2-(piperid-2-yl)-2-phenyl-2-acetamide (0.5 g) prepared by, e.g. the method of Hartmann, U.S. Patent 2,507,631, is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 8 and 1 ml cell extract of amidase. The reaction is maintained at  $30^\circ \text{C}$  until the enantiomer excess as determined by chiral chromatography is no less than 98% of D-ritalinic acid, generally about 5 hours under these conditions. An amidase with opposite stereoselectivity obtained from a microorganism such as *Rhodococcus rhodochrous* can be used to resolve DL-threo-2-(piperid-2-yl)-2-phenyl-acetamide to L-ritalinic acid and

the D-threo-2-(piperid-2-yl)-2-phenyl-acetamide. This amide is then hydrolyzed to the D-ritalinic acid by conventional means.

### EXAMPLE 3

- 5 Preparation of D-threo-2-(piperid-2-yl)-2-phenyl acetic acid from trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one

Racemic trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one (0.5 g) is added to a mixture of 20 ml 50 mM phosphate buffer pH 7.5 and 1 ml of *Pseudomonas putida* cell extract.

- 10 The reaction is maintained at 30° C until the enantiomeric excess as determined by chiral chromatography is no less than 98% D-ritalinic acid, generally about 24 hours under these conditions. Alternatively, a cell extract containing an amidase of opposite stereoselectivity may be used to
- 15 effect a resolution of racemic trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one where L-ritalinic acid is produced and the D-lactam is isolated as the product.

#### Isolation of D-lactam

- The reaction mixture prepared above is extracted
- 20 with methylene chloride and the organic layer dried with MgSO<sub>4</sub>. The organic layer is then filtered and concentration by rotary evaporation at 30° with reduced pressure, to yield an oil. The oil product may be further purified by column chromatography.

### 25 EXAMPLE 4

Preparation of D-threo-2-(piperid-2-yl)-2-phenyl-acetic acid from threo-2-(piperid-2-yl)-2-phenyl-acetonitrile

- Nitrile hydratase and amidase are obtained from *Alcaligenes faecalis* grown on 30 mM 2-cyanobutane or 2-
- 30 phenylacetonitrile as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 30 mM 2-cyanobutane is inoculated with *Alcaligenes faecalis*. After the mixture is incubated at 30°C for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with
- 35 30 mM 2-cyanobutane or 2-phenylacetonitrile. After 40 hours

15

of incubation at 30°C, the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer pH 7.5 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed  
5 through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

Racemic threo-2-(piperid-2-yl)-2-phenyl-2-  
10 acetonitrile (0.5 g) is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 8 and 1 ml cell extract of *Alcaligenes faecalis* with nitrile hydratase and amidase activity. The reaction is maintained at 30°C until the enantiomer excess as determined by chiral chromatography is  
15 no less than 98% of D-ritalinic acid, generally about 5 hours under these conditions.

#### EXAMPLE 5

The use of an esterase/lipase for the stereoselective enrichment of DL-threo- $\alpha$ -phenyl- $\alpha$ -piperidyl-acetic acid  
20 methyl ester

A microbial source of a stereoselective esterase or lipase may be obtained from commercial sources such as Novo Nordisk's "Humicola lipolase" or an ATCC *Pseudomonas* strain 31809 or 31808. Esterase/lipase is obtained from  
25 *Pseudomonas* sp. ATCC strain 31809 grown on 1% olive oil in media A supplemented with 8g/l nutrient broth. Fifty ml of media A containing the 1% olive oil and 8g/l nutrient broth is inoculated with *Pseudomonas* sp. ATCC strain 31809. After the mixture is incubated at 30°C for 48 hours, 10 ml of the  
30 mixture are subcultured into 250 ml of media with 1% olive oil supplemented with 8g/l nutrient broth. After 24 hours of incubation at 30°C, the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer, pH 7.5 and again concentrated to a paste.  
35 Cells are ruptured as above.

DL-threo- $\alpha$ -phenyl- $\alpha$ -piperidylacetic acid methyl ester (0.5g) prepared by the method of Hartmann is added to

a mixture of 20 ml of 50 mM potassium phosphate buffer pH 7 and 1 ml cell extract. The reaction is maintained at 30°C until the enantiomeric excess, as determined by chiral chromatography, is no less than 98% D-threo-methylphenidate, 5 generally in about 25 hours under these conditions.

#### PREPARATION OF EXEMPLARY DOSAGE FORMS

##### EXAMPLE 6

Tablets for chewing, each containing 5 milligrams of D-threo-methylphenidate, can be prepared in the following manner:

##### Composition (for 1000 tablets)

	D-threo-methylphenidate	5.00 grams
	mannitol	15.33 grams
	lactose	10.00 grams
15	talc	1.40 grams
	glycine	0.83 grams
	stearic acid	0.66 grams
	saccharin	0.10 grams
	5% gelatin solution	q.s.

20 The solid ingredients are each forced through a 0.25 mm mesh sieve. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a 2 mm mesh sieve, dried at 50°C and forced through a 1.7 mm mesh sieve. The D-threo-methylphenidate, glycine 25 and saccharin are carefully mixed, the granulated mannitol and lactose, stearic acid and talc added and the whole mixed thoroughly. The mass is compressed to form tablets of approximately 5 mm diameter which are concave on both sides and have a breaking groove on the one side.

##### 30 EXAMPLE 7

Tablets, each containing 10 milligrams of D-threo-methylphenidate, can be prepared in the following manner:

##### Composition (for 1000 tablets)

	D-threo-methylphenidate	10.0 grams
35	lactose	328.5 grams



corn starch	17.5	grams
polyethylene glycol 6000	5.0	grams
talc	25.0	grams
magnesium stearate	4.0	grams
5 <u>demineralized water</u>	q.s.	

The solid ingredients are first forced through a 0.6 mm mesh sieve. Then the d-threo-methylphenidate, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended  
10 in 65 milliliters of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 milliliters of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is  
15 dried overnight at 35°C, forced through a sieve of 1.2 mm mesh and compressed to form tablets of approximately 5 mm diameter which are concave on both sides and have a breaking notch on the upper side.

**EXAMPLE 8**

20 Gelatin dry-filled capsules, each containing 20 milligrams of D-threo-methylphenidate, can be prepared in the following manner:

Composition (for 1000 capsules)

D-threo-methylphenidate	20.0	grams
25 microcrystalline cellulose	6.0	grams
sodium lauryl sulfate	0.4	grams
magnesium stearate	1.6	grams

The sodium lauryl sulfate is sieved into the D-threo-methylphenidate through a 0.2 mm mesh sieve and the  
30 two components intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a 0.9 mm mesh sieve and the whole again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a 0.8 mm mesh sieve and, after mixing for a further 3 minutes, the  
35 mixture is introduced in portions of 28 milligrams each into gelatin dry-fill capsules.

**EXAMPLE 9**

A 0.2% injectable or infusible solution can be prepared, in the following exemplary manner:

TO190  
d-threo-methylphenidate 5.0 grams  
5 sodium chloride 22.5 grams  
phosphate buffer pH7.4 300.0 grams  
demineralized water to 2500 ml.

The d-threo-methylphenidate is dissolved in 1000 milliliters of water and filtered through a microfilter or  
10 slurried in 1000 ml of H<sub>2</sub>O. The buffer solution is added and the whole is made up to 2500 milliliters with water. To prepare unit dosage forms, portions of 1.0 or 2.5 milliliters each are introduced into glass ampoules such that each contains, respectively 2.0 or 5.0 milligrams of d-  
15 threo-methylphenidate.